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(54) Title: METHOD OF DELIVERING A CHEMOTHERAPEUTIC AGENT TO A SOLID TUMOR

(57) Abstract: The present invention relates to a method of treating a patient suffering from a solid tumor, for example, a deep surgically-inoperable brain tumor, a breast tumor, a tumor of the prostate, etc. The method comprises administering to the peritumoral tissue an effective amount of a sustained release composition comprising a biocompatible polymer and at least one chemotherapeutic agent dispersed within the polymer.

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METHOD OF DELIVERING A CHEMOTHERAPEUTIC AGENT TO A SOLID TUMOR

BACKGROUND OF THE INVENTION

Over the past 30 years, fundamental advances in the chemotherapy of
5 neoplastic disease have been realized. However, despite the impressive advances
that have been made, many of the most prevalent forms of human cancer, for
example, solid tumors of the brain, prostate, breast, etc. still resist effective
chemotherapeutic intervention.

For example, in 1999, over 100,00 people in the United States were
10 diagnosed with a primary or metastatic brain tumor, and the incidence is on the rise.
Brain tumors are very often fatal. Chemotherapy is often ineffective against these
tumors due, in large part, to the difficulty in achieving therapeutically effective
levels of chemotherapeutic agents in the area of tumor growth and infiltration. For
example, the existence of the blood brain barrier (BBB) can restrict the flow of
15 certain chemotherapeutic agents from the cerebral capillaries to the brain.

Methods of treating brain tumors have included the delivery of
chemotherapeutics directly to the surgical cavity resulting from surgical debulking of
the tumor or intratumorally. For example, the use of polymer wafers containing
N,N'-Bis(2-chloroethyl)-N-nitrosourea (BCNU), have shown limited efficacy in the
20 treatment of gliomas when the wafers are placed in the surgical cavity resulting from
a glioma debulking.

Even solid tumor therapies, which are not restricted by the existence of the
blood brain barrier, can give unsatisfactory results. For example, prostate cancer is a
common form of cancer among males. Clinical evidence shows that human prostate
25 cancer has the propensity to metastasize to bone and is currently the second leading
cause of cancer death, after lung cancer, among men. Commonly, treatment is based
on surgery and/or radiation therapy, but these methods give unsatisfactory results in
a significant percentage of cases.

Yet another prevalent type of solid tumor is a tumor of the breast. Breast
30 cancer is the most common form of cancer in women in the United States. Both its

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cause and the means for its cure remain undiscovered. In 2000, 182,800 new cases of female invasive breast cancer are expected to be diagnosed, and 40,800 women are expected to die from the disease. Breast cancer is the second leading cause of cancer death for all women, and the leading overall cause of death in women between the ages of 40 and 55.

It is clear that there is a need for improvements in current therapies for the treatment of cancer, in particular cancers involving solid tumors.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating a patient suffering from a solid tumor, such as a tumor of the brain, prostate, breast, lung, colon, uterus, skin, liver, bone, pancreas, ovary, testes, bladder, kidney, head, neck, stomach, cervix, rectum, larynx, or esophagus. The method comprises administering to the peritumoral tissue an effective amount of a sustained release composition comprising a biocompatible polymer and at least one chemotherapeutic agent dispersed within the polymer.

In a particular embodiment, the sustained release composition is in the form of microparticles. Preferably, the microparticles can be administered by injection into peritumoral tissue.

20 The chemotherapeutic agent can be any agent which is therapeutically effective. Combinations of chemotherapeutic agents can also be present in the sustained release device.

The polymer of the sustained release composition can be any biocompatible polymer. In a particular embodiment, the polymer is biodegradable.

25 The administration of the sustained release composition into the peritumoral tissue rather than directly into the tumor provides increased therapeutic benefits, for example, increased survival. In addition, when the choice of sustained release composition is in the form of microparticles, administration can be accomplished by injection, resulting in a minimally invasive procedure.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a plot of *in vitro* release of carboplatin from PLG microparticles containing carboplatin at loading densities of 10, 15 or 20%, versus time over a 21 day period.

5 Figure 2 is a plot of the *in vitro* cytotoxicity of RG2 cells following 72 hours of exposure to microparticles containing carboplatin, versus a bolus of carboplatin at the indicated doses.

10 Figure 3A is a plot of the amount of carboplatin present in healthy brain tissue at 0-0.5 mm distance from the site of injection, following administration of microparticles containing carboplatin and an equivalent dose of a carboplatin bolus, versus time post administration.

15 Figure 3B is a plot of the amount of carboplatin present in healthy brain tissue at 0.5-1.5 mm distance from the site of injection, following administration of microparticles containing carboplatin and an equivalent dose of a carboplatin bolus, versus time post administration.

20 Figure 4 is a plot of the % survival for treatment groups receiving specified amounts of microparticles containing carboplatin, and a bolus injection of carboplatin directly into the center of an 8 day old striatal tumor, versus time post tumor implantation in days. The survival curve for animals with no treatment is also shown.

 Figure 5 is a plot of the % survival for treatment groups receiving specified amounts of microparticles containing carboplatin, and a bolus injection of a carboplatin at three predetermined sites (triangle formation) of the peritumoral tissue. The survival curve for animals with no treatment is also shown.

25 Figure 6 is a plot of the % survival for treatment groups receiving specified amounts of microparticles containing BCNU, and a bolus injection of BCNU directly into the center of an 8 day old striatal tumor, versus time post tumor implantation in days. The survival curve for animals with no treatment is also shown.

30 Figure 7 is a plot of the % survival for treatment groups receiving specified amounts of microparticles containing BCNU, and a bolus injection of a BCNU at

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three predetermined sites (triangle formation) of the peritumoral tissue. The survival curve for animals with no treatment is also shown.

Figure 8 is a set of graphs showing the effects of bolus and sustained release carboplatin, injected either into the tumor center or into the peritumoral tissue, on the suppression of growth of MATB-III tumors implanted into the subcutaneous space of rats.

Figure 9 is a set of graphs showing the effects of bolus and sustained release 5-FU, injected either into the tumor center or the peritumoral tissue, on the suppression of growth of MATB-III tumors grown in the subcutaneous space of rats.

Figure 10 is a graph showing the effects of sequential injections into the peritumoral tissue (14 days following the first treatment) of sustained release carboplatin or 5FU microparticles on the growth of MATB-III tumors.

DETAILED DESCRIPTION OF THE INVENTION

The foregoing and other objects, features and advantages of the invention will now be more particularly described with reference to the accompanying drawings and pointed out in the claims. It is understood that the particular embodiments of the invention are shown by way of illustration and not as limitations of the invention. The principles of the invention can be employed in various embodiments without departing from the scope of the invention. A description of the preferred embodiments of the invention follows.

"Solid tumor", as that term is used herein, refers to any tumor which forms a mass. Examples of solid tumors include, but are not limited to, tumors of the brain, prostate, breast, colon, lung, kidney, bladder, liver, bone, head, neck, stomach, larynx, esophagus, cervix, rectum, uterus, skin (e.g., melanomas), endometrium, pancreas and testes.

"Brain tumor" or "tumors of the brain", as that term is used herein, refers to primary and metastatic brain tumors. Gliomas are primary brain tumors which arise from the glial cells in the brain and spinal cord, and are the most common primary brain tumors. Gliomas are classified into several groups based on the type of glial cell involved. For example, astrocytomas, which are the most common type of gliomas, are developed from astrocytes. Types of astrocytomas include well-

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differentiated, anaplastic, and glioblastoma multiforme. Other types of glioma include ependymomas, oligodendrogliomas, ganglioneuromas, mixed gliomas, brain stem gliomas, optic nerve gliomas, meningiomas, pineal tumors, pituitary adenomas, and primitive neuroectodermal tumors, such as medulloblastomas, neuroblastomas, pineoblastomas, medulloepitheliomas, ependymblastomas and polar spongioblastomas. Non-glioma type tumors include chordomas and craniopharyngiomas.

In a specific embodiment, the tumor is a deep, surgically-inoperable tumor. For example, a deep, surgically-inoperable glioma.

Administration into the tissue of the peritumoral area can be accomplished by a single administration, by multiple administrations into a single site, by multiple administrations into multiple sites or combinations thereof. Multiple injections can also be spread out over time for instance over days or weeks. Administration can be accomplished by, for example, injection or surgical implantation. For example, stereotactic injection or implantation is suitable. Importantly, administration is into the peritumoral area rather than directly into the tumor.

"Injection" as that term is used herein, includes administration through a delivery port alone or in combination with a surgical scope such as a laparoscope, endoscope, laryngoscope, cystoscope, proctoscope or thoracoscope. The delivery port can be, for example, a surgical tube such as a catheter with an appropriately sized bore, or a needle or needle-like port. As such, delivery can include a minor incision in the patient to permit entry of a delivery port, such as a needle or catheter, or a combination of a delivery port and a surgical scope. Advantageously, injection of the composition avoids the need for an open surgical procedure to expose the treatment area.

"Patient" as that term is used herein refers to the recipient of the treatment. Mammalian and non-mammalian patients are included. In a specific embodiment, the patient is a mammal, such as a human, canine, murine, feline, bovine, ovine, swine or caprine. In a preferred embodiment, the patient is a human.

"Peritumoral area", as that term is used herein, is the outermost edge or perimeter of the tumor and tissue which is within 3 cms outward of the outermost edge of the tumor, and 1 cm inward of the outermost edge. Preferably the area is

within 2 cms outward of the outermost edge of the tumor and 1 cm inward of the outermost edge.

"Bolus injection", as that term is used herein, is an injection of a solution of a chemotherapeutic agent which is not present in a sustained release composition.

5 The term "sustained release composition" as defined herein, comprises a biocompatible polymer having incorporated therein at least one chemotherapeutic agent. Suitable biocompatible polymers, can be either biodegradable or non-biodegradable polymers or blends or copolymers thereof, as described herein.

10 Typically, the sustained release composition can contain from about 0.01% (w/w) to about 50% (w/w) of the chemotherapeutic agent (dry weight of composition). The amount of agent used will vary depending upon the desired effect of the agent, the planned release levels, and the time span over which the agent will be released. A preferred range of agent loading is between about 0.1% (w/w) to about 30% (w/w) agent. A more preferred range of agent loading is between about
15 0.5% (w/w) to about 20% (w/w) agent.

 The sustained release compositions of this invention can be formed into many shapes such as a film, a pellet, a rod, a filament, a cylinder, a disc, a wafer or a microparticle. A microparticle is preferred. A "microparticle" as defined herein, comprises a polymer component having a diameter of less than about one millimeter
20 and having a chemotherapeutic agent dispersed therein. A microparticle can have a spherical, non-spherical or irregular shape. Typically, the microparticle will be of a size suitable for injection. A preferred size range for microparticles is from about one to about 180 microns in diameter.

 As defined herein, a sustained release of chemotherapeutic agent is a release
25 of the agent from a sustained release composition. The release occurs over a period which is longer than that period during which a therapeutically significant amount of the chemotherapeutic agent, would be available following direct administration of a solution of the chemotherapeutic agent. It is preferred that a sustained release be a release of chemotherapeutic agent which occurs over a period of greater than two
30 days. A sustained release of chemotherapeutic agent, from a sustained release composition can be a continuous or a discontinuous release, with relatively constant or varying rates of release. The continuity of release and level of release can be

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affected by the type of polymer composition used (e.g., monomer ratios, molecular weight, and varying combinations of polymers), agent loading, and/or selection of excipients to produce the desired effect.

A "therapeutically effective amount", as used herein, is the amount of the composition for the sustained release of a chemotherapeutic agent, necessary to elicit the desired biological response following administration. In the instant invention, the desired biological response is prevention or reduction in the progression of a solid tumor, or reversal partially or totally of the developed solid tumor. It is understood that by treating the solid tumor that survival time of the patient can be prolonged. Dosage can be optimized depending on the size of the sustained release composition, the location and size of the solid tumor to be treated and the period over which the drug will be delivered.

Chemotherapeutic agents suitable for use in the invention include any chemotherapeutic. Classes of chemotherapeutics include, but are not limited to, antimetabolites, cytotoxic agents, immunomodulators, antibiotic derivatives and nitrogen mustard derivatives, antiangiogenic agents, receptor antagonists, receptor ligands, stimulators, and viral vectors. In a particular embodiment, the chemotherapeutic agent has limited ability to cross the blood brain barrier. Combinations of chemotherapeutic agent can also be present in the sustained release composition. Specific agents include, but are not limited to, carboplatin, cisplatin, adriamycin, doxorubicin, carmustine (also referred to in the art as N,N'-Bis(2-chloroethyl)-N-nitrosourea, BCNU and BiCNU), lomustine (also referred to in the art as N-(2-chloroethyl)-N-cyclohexyl-N-nitrosourea and CCNU), etoposide, teniposide, 0⁶-benzylguanine, paclitaxel, methotrexate, vincristine, vinblastine, vinorelbine, gemcitabine, cyclophosphamide, temazepam, 5-fluorouracil and 4-HC.

The sustained release composition can contain other biologically active agents which impart a beneficial effect. For example, anti-inflammatory agents, antibacterial agents and/or antiviral agents can be present in the composition. In addition, the method described herein can be combined with other cancer therapies, such as, radiation therapy.

The chemotherapeutic agent of the sustained release composition can be

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stabilized against degradation, loss of potency and/or loss of biological activity, all of which can occur during formation of the sustained release composition and/or prior to and during *in vivo* release of the chemotherapeutic agent. In one embodiment, stabilization can result in a decrease in the solubility of a chemotherapeutic agent, the consequence of which is a reduction in the initial release of agent. In addition, the period of release of the agent can be prolonged.

Stabilization of the chemotherapeutic agent can be accomplished, for example, by the use of a stabilizing agent. "Stabilizing agent", as that term is used herein, is any agent which binds or interacts in a covalent or non-covalent manner or is included with the chemotherapeutic agent. Stabilizing agents suitable for use in the invention are described in co-pending U.S. Patent Application 08/934,830 to Burke *et al.*, filed on September 22, 1997 and U.S. Patent Nos. 5,711,968 to Tracy *et al.*, 5,654,010 and 5,667,808 to Johnson *et al.*, and 5,716,644 and 5,674,534 to Zale *et al.*, the entire teachings of which are incorporated herein by reference.

For example, a metal cation can be complexed with the chemotherapeutic agent, or the chemotherapeutic agent can be complexed with a polycationic complexing agent such as protamine, albumin, spermidine and spermine, or associated with a "salting-out" salt.

20 Suitable metal cations include any metal cation capable of complexing with the agent. A metal cation-stabilized chemotherapeutic agent, as defined herein, comprises a chemotherapeutic agent and at least one type of metal cation wherein the cation is not significantly oxidizing to the agent. In a particular embodiment, the metal cation is multivalent, for example, having a valency of +2 or more.

25 Suitable stabilizing metal cations include biocompatible metal cations. A metal cation is biocompatible if the cation is non-toxic to the recipient, in the quantities used, and also presents no significant deleterious or untoward effects on the recipient's body, such as a significant immunological reaction at the injection site. The suitability of metal cations for stabilizing chemotherapeutic agents and the ratio of metal cation to chemotherapeutic agent needed can be determined by one of
30 ordinary skill in the art by performing a variety of stability indicating techniques, for example, HPLC analyses (e.g., Size Exclusion, Reversed Phase and other Ion Exchange) on particles of metal cation-stabilized chemotherapeutic agents. The

molar ratio of metal cation to agent is typically between about 1:2 and about 100:1, preferably between about 2:1 and about 10:1.

Examples of stabilizing metal cations include, but are not limited to, K^+ , Zn^{+2} , Mg^{+2} and Ca^{+2} . Stabilizing metal cations also include cations of transition metals, such as Cu^{+2} . Combinations of metal cations can also be employed.

The chemotherapeutic agent can also be stabilized with at least one polycationic complexing agent. Suitable polycationic complexing agents include, but are not limited to, protamine, and albumin. The suitability of polycationic complexing agents for stabilizing chemotherapeutic agents can be determined by one of ordinary skill in the art in the manner described above for stabilization with a metal cation. An equal weight ratio of polycationic complexing agent to chemotherapeutic agent is suitable.

A polymer is biocompatible if the polymer and any degradation products of the polymer are non-toxic to the recipient and also possess no significant deleterious or untoward effects on the recipient's body, such as a significant chronic immunological reaction at the injection site.

"Biodegradable", as defined herein, means the composition will degrade or erode *in vivo* to form smaller chemical species. Degradation can result, for example, by enzymatic, chemical and/or physical processes. Suitable biocompatible, biodegradable polymers include, for example, poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, poly(caprolactone), polycarbonates, polyesteramides, polyanhydrides, poly(amino acid)s, poly(ortho ester)s, polyacetals, polycyanoacrylates, polyamides, polyacetals, poly(ether ester)s, copolymers of poly(ethylene glycol) and poly(ortho ester)s, poly(dioxanone)s, poly(alkylene alkylate)s, biodegradable polyurethanes, blends or copolymers thereof.

Biocompatible, non-biodegradable polymers suitable for use in the invention, include, for example, polyacrylates, polymers of ethylene-vinyl acetates and acyl substituted cellulose acetates, non-degradable polyurethanes, polystyrenes, polyvinyl chloride, polyvinyl fluoride, poly(vinyl imidazole), chlorosulphonate polyolefins, polyethylene oxide, blends and copolymers thereof.

Further, the terminal functionalities or pendant groups of the polymers can be

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modified, for example, to modify hydrophobicity, hydrophilicity and/or provide, remove or block moieties which can interact with the active agent (via, for example ionic or hydrogen bonding).

Acceptable molecular weights for polymers used in this invention can be determined by a person of ordinary skill in the art taking into consideration factors such as the desired polymer degradation rate, physical properties such as mechanical strength, and rate of dissolution of polymer in solvent and viscosity. Typically, an acceptable range of molecular weight is about 2,000 Daltons to about 2,000,000 Daltons. In a preferred embodiment, the polymer is a biodegradable polymer or copolymer. In a more preferred embodiment, the polymer is poly(lactide-co-glycolide) (hereinafter "PLG").

The sustained release composition can contain excipients. These excipients are added to maintain the potency of the chemotherapeutic agent over the duration of release and modify polymer degradation. Suitable excipients include, for example, carbohydrates, amino acids, fatty acids, surfactants, and bulking agents, and are known to those skilled in the art. The amount of excipient used is based on ratio to the chemotherapeutic agent, on a weight basis. For amino acids, fatty acids and carbohydrates, such as sucrose, lactose, mannitol, dextran and heparin, the ratio of carbohydrate to chemotherapeutic agent, is typically between about 1:10 and about 20:1. For surfactants, such as TWEEN™ and PLURONIC™, the ratio of surfactant to chemotherapeutic agent is typically between about 1:1000 and about 1:20.

Bulking agents typically comprise inert materials. Suitable bulking agents are known to those skilled in the art.

The excipient can also be a metal cation component which is separately dispersed within the polymer matrix. This metal cation component acts to modulate the release of the chemotherapeutic agent, by for example, modifying polymer degradation and is not complexed with the chemotherapeutic agent. The metal cation component can optionally contain the same species of metal cation, as is contained in the metal cation stabilized chemotherapeutic agent, and/or can contain one or more different species of metal cation. The metal cation component acts to modulate the release of the chemotherapeutic agent from the polymer matrix of the sustained release composition and can enhance the stability of the chemotherapeutic

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agent in the composition. A metal cation component used in modulating release typically comprises at least one type of multivalent metal cation. Examples of metal cation components suitable to modulate release include or contain, for example, Mg(OH)₂, MgCO₃ (such as 4MgCO₃·Mg(OH)₂·5H₂O), MgSO₄, Zn(OAc)₂,
5 Mg(OAc)₂, ZnCO₃ (such as 3Zn(OH)₂·2ZnCO₃), ZnSO₄, ZnCl₂, MgCl₂, CaCO₃, zinc citrate and magnesium citrate. A suitable ratio of metal cation component to polymer is between about 1:99 to about 1:2 by weight. The optimum ratio depends upon the polymer and the metal cation component utilized. A polymer matrix containing a dispersed metal cation component to modulate the release of a
10 biologically active agent from the polymer matrix is further described in U.S. Patent Nos. 5,656,297 and 5,912,015 to Bernstein *et al.*, the teachings of both of which are incorporated herein by reference in their entirety.

In yet another embodiment, at least one pore forming agent, such as a water soluble salt, sugar or amino acid, is included in the sustained release composition to
15 modify the microstructure. The proportion of pore forming agent is between about 1% (w/w) to about 30% (w/w). It is preferred that at least one pore forming agent be included in a nonbiodegradable polymer matrix of the present invention.

A number of methods are known by which compounds can be encapsulated in the form of microparticles. In many of these processes, the material to be
20 encapsulated is dispersed in a solvent containing a wall forming material. At a single stage of the process, solvent is removed from the microparticles and thereafter the microparticle product is obtained.

An example of a conventional microencapsulation process and microparticles produced thereby is disclosed in U.S. Pat. No. 3,737,337,
25 incorporated by reference herein in its entirety, wherein a solution of a wall or shell forming polymeric material in a solvent is prepared. The solvent is only partially miscible in water. A solid or core material is dissolved or dispersed in the polymer-containing solution and, thereafter, the core material-containing solution is dispersed in an aqueous liquid that is immiscible in the organic solvent in order to remove
30 solvent from the microparticles.

Another example of a process in which solvent is removed from microparticles containing a substance is disclosed in U.S. Pat. No. 3,523,906,

incorporated herein by reference in its entirety. In this process a material to be encapsulated is emulsified in a solution of a polymeric material in a solvent that is immiscible in water and then the emulsion is emulsified in an aqueous solution containing a hydrophilic colloid. Solvent removal from the microparticles is then accomplished by evaporation and the product is obtained.

In still another process as shown in U.S. Pat. No. 3,691,090, incorporated herein by reference in its entirety, organic solvent is evaporated from a dispersion of microparticles in an aqueous medium, preferably under reduced pressure.

Similarly, the disclosure of U.S. Pat. No. 3,891,570, incorporated herein by
10 reference in its entirety, shows a method in which solvent from a dispersion of microparticles in a polyhydric alcohol medium is evaporated from the microparticles by the application of heat or by subjecting the microparticles to reduced pressure.

Another example of a solvent removal process is shown in U.S. Pat. No. 3,960,757, incorporated herein by reference in its entirety.

15 Tice *et al.*, in U.S. Pat. No. 4,389,330, incorporated herein by reference in its entirety, describe the preparation of microparticles containing an active agent by a method comprising: (A) dissolving or dispersing an active agent in a solvent and dissolving a wall forming material in that solvent; (b) dispersing the solvent containing the active agent and wall forming material in a continuous-phase
20 processing medium; (c) evaporating a portion of the solvent from the dispersion of step (b), thereby forming microparticles containing the active agent in the suspension; and (d) extracting the remainder of the solvent from the microparticles.

Other methods for forming a composition for the sustained release of a chemotherapeutic agent are described in U.S. Patent No. 5,019,400, issued to
25 Gombotz *et al.*, and U.S. Patent 5,922,253 issued to Herbert *et al.*, the teachings of which are incorporated herein by reference in their entirety.

In this method, a mixture comprising at least one chemotherapeutic agent, at least one biocompatible polymer and at least one polymer solvent is processed to create droplets, wherein at least a significant portion of the droplets contains
30 polymer, polymer solvent and the agent. These droplets are then frozen by a suitable means. Examples of means for processing the suspension to form droplets include directing the dispersion through an ultrasonic nozzle, pressure nozzle, Rayleigh jet,

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or by other known means for creating droplets from a solution.

Means suitable for freezing droplets include directing the droplets into or near a liquified gas, such as liquid argon or liquid nitrogen to form frozen microdroplets which are then separated from the liquid gas. The frozen
5 microdroplets are then exposed to a liquid or solid non-solvent, such as ethanol, hexane, ethanol mixed with hexane, heptane, ethanol mixed with heptane, pentane or oil.

The solvent in the frozen microdroplets is extracted as a solid and/or liquid into the non-solvent to form a polymer/chemotherapeutic agent matrix comprising a
10 biocompatible polymer and a chemotherapeutic agent. Mixing ethanol with other non-solvents, such as hexane, heptane or pentane, can increase the rate of solvent extraction, above that achieved by ethanol alone, from certain polymers, such as poly(lactide-co-glycolide) polymers.

A wide range of sizes of sustained release compositions can be made by
15 varying the droplet size, for example, by changing the ultrasonic nozzle diameter. If the sustained release composition is in the form of microparticles, and very large microparticles are desired, the microparticles can be extruded, for example, through a syringe directly into the cold liquid. Increasing the viscosity of the polymer solution can also increase microparticle size. The size of the microparticles which
20 can be produced by this process ranges, for example, from greater than about 1000 to about 1 micrometers in diameter.

Yet another method of forming a sustained release composition, from a suspension comprising a biocompatible polymer and a chemotherapeutic agent, includes film casting, such as in a mold, to form a film or a shape. For instance,
25 after putting the suspension into a mold, the polymer solvent is then removed by means known in the art, or the temperature of the polymer suspension is reduced, until a film or shape, with a consistent dry weight, is obtained.

Without being bound by a particular theory it is believed that the release of the chemotherapeutic agent can occur by two different mechanisms. First, the agent
30 can be released by diffusion through aqueous filled channels generated in the polymer matrix, such as by the dissolution of the agent, or by voids created by the removal of the polymer solvent during the preparation of the sustained release

composition. A second mechanism is the release of the agent, due to degradation of the polymer. The rate of degradation can be controlled by changing polymer properties that influence the rate of hydration of the polymer. These properties include, for instance, the ratio of different monomers, such as lactide and glycolide, comprising a polymer; the use of the L-isomer of a monomer instead of a racemic mixture; and the molecular weight of the polymer. These properties can affect hydrophilicity and crystallinity, which control the rate of hydration of the polymer. Hydrophilic excipients such as salts, carbohydrates, and surfactants can also be incorporated to increase hydration which can alter the rate of erosion of the polymer.

By altering the properties of the polymer, the contributions of diffusion and/or polymer degradation to agent release can be controlled. For example, increasing the glycolide content of a poly(lactide-co-glycolide) polymer and decreasing the molecular weight of the polymer can enhance the hydrolysis of the polymer, and thus provides an increased chemotherapeutic agent release from polymer erosion.

In addition, the rate of polymer hydrolysis is increased in non-neutral pH. Therefore, an acidic or a basic excipient can be added to the polymer suspension, used to form the sustained release composition, for example, microparticles, to alter the polymer erosion rate.

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EXPERIMENTAL METHODS

SUBJECTS

Male Fischer rats (170 - 220g; Taconic Farms, Germantown, NY) were used in all studies. The rats were housed in pairs in polypropylene cages with free access to food and water. The vivarium was maintained on a 12 h light:12 h dark cycle with a room temperature of $22^{\circ}\text{C} \pm 1$, and relative humidity level of $50\% \pm 5\%$. All procedures complied with NIH Guidelines.

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EXAMPLE 1: TUMOR CELL IMPLANTATION

Rat glioma (RG2) cells were maintained as a monolayer culture in F10 medium (GIBCO, Grant Island, NY) with iron supplemented 10% calf serum until confluent (3-5 days). On the day of implantation, the cells were suspended in F10

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medium with 1.2% methylcellulose (Sigma, St. Louis, MO). Immediately prior to implantation of RG2 cells into the brain, rats were anesthetized using an intramuscular injection of a solution containing ketamine (24 mg/mL), xylazine (1.3 mg/mL) and acepromizine (0.33 mg/mL) and placed in a stereotaxic instrument. Using a stereotaxic-mounted 10 μ L Hamilton syringe with a 22 gauge needle, RG2 cells were injected unilaterally into the striatum (5×10^4 cells/ 5μ L) at the following coordinates: A-P (+2.0 mm), L (+3.0 mm) and V (-6.5 mm).

EXAMPLE 2: FABRICATION AND IMPLANTATION OF CARBOPLATIN-LOADED PLG MICROPARTICLES

Poly(lactide-co-glycolide) (PLG, Medisorb® 50/50 DL, low MW=10K, Alkermes Inc., Wilmington, Ohio) microparticles were fabricated with a carboplatin loading density of 10% (w/w). PLG (1.70 g) was dissolved in methylene chloride (3 g). To this solution was added 170 mg of ground/sieved carboplatin (<5 μ m), and the mixture was shaken vigorously and sonicated. 100 mL of a 1% PVA solution was then added and the mixture was homogenized at about 12,000 rpm for approximately 3 minutes. The resulting suspension was then quickly heated in a water bath (approximately 50°C) with stirring at about 550 rpm. After 15 minutes, the carboplatin-containing microparticles were collected by filtration, sieved through 70 μ m and 40 μ m screens and rinsed with water. The microparticles were then frozen at -70°C and lyophilized under 50 μ Torr for 2 days. Blank microparticles were prepared using the same procedure except that carboplatin was not present.

For implantation into the brain, the microparticles were suspended in a solution containing 0.9% saline, 0.5% Tween and 3.0% carboxymethylcellulose (low viscosity). All suspensions were prepared to yield a final concentration of 10% PLG weight/volume. The microparticle suspension was injected using a Hamilton syringe with a 23 gauge needle attached. All injections were delivered at a rate of 2 μ L/minute and the injection cannula was left in place for an additional two minutes to allow the suspension to diffuse from the needle tip.

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EXAMPLE 3: *IN VITRO* CYTOTOXICITY OF CARBOPLATIN-CONTAINING MICROPARTICLES

To determine the cytotoxicity of carboplatin on RG2 cells, a commercially-available kit (CyQuant Cell Proliferation Assay Kit; Molecular Probes, Inc., Eugene, OR) was used to determine cell numbers by quantifying the amount of fluorescent dye bound to cellular nucleic acids. RG2 cells were plated in 48-well dishes at a density of 200K/well in 0.5 ml of medium. Twenty four hours later, carboplatin was added to the wells at concentrations ranging from 2.5-100 μ g/ml (n=6/concentration). At 72 hours after the addition of carboplatin, the cells were centrifuged at 1500g for 10 minutes at 4°C to adhere them to the plate and the plates were frozen at -70°C until the time of assay. For quantification of cell number following carboplatin treatment, the cells were thawed and lysed in 200 μ L CyQuant Lysis Buffer/GR dye for 5 minutes and fluorescence was measured using a fluorescence plate reader (CytoFluor II; Perseptive Biosystems, Framingham, MA) with excitation set at 485 nm and emission detection set at 530 nm. Fluorescence was converted to cell number by comparison to a standard curve relating fluorescence to known concentrations of RG2 cells. The results are represented graphically in Figure 2.

20 **EXAMPLE 4: *IN VITRO* RELEASE FROM CARBOPLATIN-CONTAINING PARTICLES**

For determination of the *in vitro* release of carboplatin from carboplatin-containing microparticles over time, 10 mg of microparticles containing a 10% load of carboplatin (1 mg carboplatin) were mixed with 1 mL of PBS and incubated at
25 37°C. At 1 hour, 8 hours, 1 day, 3 days, 7 days, 14 days, and 21 days (n=3/time point), supernatant was removed. All samples were frozen at -80°C and platinum levels were determined by atomic adsorption spectroscopy. To verify the total amount of carboplatin loaded into the microparticles, 10 mg of the PLG microparticles were dissolved in 1 mL of methylene chloride. The results are
30 represented graphically in Figure 1.

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EXAMPLE 5: *IN VIVO* RELEASE AND DIFFUSION FROM CARBOPLATIN-CONTAINING MICROPARTICLES

For determination of the *in vivo* release and diffusion of carboplatin from carboplatin-containing microparticles over time, 1 mg of microparticles containing a 10% load of carboplatin (100 µg carboplatin) was injected unilaterally into the striatum. A separate series of animals received a bolus injection of carboplatin (100 µg) into the same site. At 1 minute, 1 hour, 1 day, 3 days, 7 days, 14 days, and 21 days post injection (n=3/time point), the brain tissue surrounding the needle tract was dissected into two discrete regions using microdissection techniques. The first section extended from the needle tract outward for 0.5 mm, and the second section extended from 0.5 mm to 1.5 mm from the needle tract. Tissue samples were digested in 0.5 ml of Soluene and incubated at 37°C for 8 hours. 0.5 mL of methylene chloride was then added to dissolve the microparticles and permit quantification of platinum levels. All tissue samples were frozen at -80°C, and platinum levels were determined by atomic adsorption spectroscopy. The results are represented graphically in Figure 3.

EXAMPLE 6: IMPLANTATION OF CARBOPLATIN-CONTAINING MICROPARTICLES INTO A MODEL OF DEEP INOPERABLE GLIOMA

The model of glioma used in these studies determined the effects of sustained release of carboplatin from the microparticles containing carboplatin on survival of animals bearing deep, surgically-inoperable tumors. The carboplatin-containing microparticles were implanted directly into a growing tumor, and also into the peritumoral tissue. RG2 cells were implanted unilaterally into the striatum. At 8 days post implantation, the animals received implants of microparticles containing carboplatin or a bolus injection of carboplatin directly into the tumor. All injections, which were made directly into the tumor, used the same coordinates for implantation of the RG2 cells (A-P (+2.0 mm), L (+3.0 mm) and V (-6.6 mm)).

Rats were assigned to one of four treatment groups: (1) 100 µg carboplatin as a bolus (n=10); (2) 10 µg of carboplatin from carboplatin-containing microparticles (n=12); (3) 50 µg of carboplatin from carboplatin-containing

microparticles (n=13); and (4) 100 µg of carboplatin from (n=10) carboplatin-containing microparticles. Control animals having no implant were also assessed. The results are presented in Table 1 and represented graphically in Figure 4.

A second group of animals was treated following the dosing regimen described below, with implantation of the carboplatin in bolus and microparticle form occurring at three sites in the peritumoral tissue. More specifically, implants were made at 3 sites surrounding the tumor which correspond to the following coordinates: A-P (+2.85 mm), L (+3.0 mm) and V (-5.5 mm); A-P (+1.15 mm), L (+2.0 mm) and V (-5.5 mm); A-P (+1.5 mm), L (+4.0 mm) and V (-5.5 mm). The total dose for each treatment group was equally divided among the three sites. Treatment groups consisted of: (1) 10 µg of carboplatin from carboplatin-containing microparticles (n=20); (2) 50 µg of carboplatin from carboplatin-containing microparticles (n=22); (3) 100 µg of carboplatin from carboplatin-containing microparticles (n=22); (4) 10 µg carboplatin bolus (n=17); (5) 50 µg carboplatin bolus (n=15); and (6) 100 µg of a carboplatin bolus (n=19). Control animals receiving no implant were also assessed. The results are presented in Table 1 and represented graphically in Figure 5.

The results suggest that animals receiving carboplatin-containing microparticles into the peritumoral tissue show enhanced survival when compared to animals receiving the same dose of carboplatin-containing microparticles directly into the tumor.

Statistical analysis was performed as follows. Survival after each treatment was analyzed using Kaplan-Meier survival curves. Non-parametric Kruskal-Wallis statistics were used to determine overall treatment effects using the day of death as the non-parametric variable (JMP, SAS Institute Inc., Cary, NC. The non-parametric modification of the Neuman-Keuls test was used for subsequent pairwise comparisons. The effects of carboplatin-loaded microparticle injections on tumor volume were compared using a one-way analysis of variance. Statistical significance in all cases was defined as $p < 0.05$.

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TABLE 1

Treatment Group	Median Survival (Days Post Tumor Implantation)	% Increase in Median Survival (Relative to No Treatment)	Maximum Survival (Days Post Tumor Implantation)	% Increase in Maximum Survival
No Treatment	18		22	
Bolus (100µg) Intratumorally	22	22	24	9
Microparticles (10µg) Intratumorally	18	0	22	0
Microparticles (50µg) Intratumorally	22	22	25	14
Microparticles (100µg) Intratumorally	25	39	27	23
Bolus (10µg) Peritumorally	18	0	23	5
Bolus (50µg) Peritumorally	22	22	26	18
Bolus (100µg) Peritumorally	26	44	34	55
Microparticles (10µg) Peritumorally	20	11	25	14
Microparticles (50µg) Peritumorally	40	122	49	123
Microparticles (100µg) Peritumorally	52	189	64	191

EXAMPLE 7: FABRICATION OF BCNU-LOADED PLG MICROPARTICLES

Poly(lactide-co-glycolide) PLG, Medisorb® 50/50 DL, MW=10KD, (Alkermes Inc., Wilmington, Ohio) microparticles were fabricated by a solvent evaporation process with a carmustine (BCNU, 1,3-bis[2-chloroethyl]-1-nitrosourea, Sigma Chemical) loading density of 10% (w/w). Initially, 1.0 gram of PLG and 110 mg of carmustine were dissolved in 7.5 grams of methylene chloride. The solution was added to a 100 mL 4-necked glass reaction flask contained 40 mL of 0.75% PVA solution mechanically stirred (Caframo, model RZR1, Warton, Ont., Canada). The organic phase was then dispersed in aqueous medium. The temperature was maintained at room temperature for 10 minutes, gradually raised to 40°C for 50 minutes by a circulating water bath and maintained at 40°C for an additional 50 minutes. After cooling to room temperature, the suspension was drained from the flask and the microparticles were collected by filtration. The microcapsules were sieved through 70 and 40 µm cell strainers, and the 40-70 µm sized fraction was collected and washed with distilled water. The microparticles were then frozen at -70°C and lyophilized under 50 µTorr for 2 days. Blank (noncarmustine-loaded) microspheres were treated in an identical manner except that carmustine was omitted from the procedure.

EXAMPLE 8: IMPLANTATION OF BCNU-CONTAINING MICROPARTICLES INTO A MODEL OF DEEP INOPERABLE GLIOMA

All animals employed in the following study received RG2 cells implanted unilaterally into the Striatum. At 8 days post implantation, the animals received BCNU-containing microparticles or a bolus injection of BCNU, either directly into the tumor, or at 3 predetermined sites in the peritumoral tissue.

Rats receiving direct intratumoral injections were assigned to one of four treatment groups: (1) 100 µg carboplatin as a bolus (n=15); (2) 10 µg of BCNU from BCNU-containing microparticles (n=15); (3) 50 µg of BCNU from BCNU-containing microparticles (n=15); and (4) 100 µg of BCNU from (n=15) BCNU-containing microparticles. Control animals having no implant were also assessed. The results are presented in Table 2 and represented graphically in Figure 6.

A second group of animals was treated following the dosing regimen

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described below, with implantation of the BCNU in bolus and microparticle form occurring at three sites in the peritumoral tissue. More specifically, implants were made at 3 sites surrounding the tumor which correspond to the following coordinates: A-P (+2.85 mm), L (+3.0 mm) and V (-5.5 mm); A-P (+1.15 mm), L (+2.0 mm) and V (-5.5 mm); A-P (+1.5 mm), L (+4.0 mm) and V (-5.5 mm). The total dose for each treatment group was equally divided among the three sites. Treatment groups consisted of: (1) 10 μ g of BCNU from BCNU-containing microparticles (n=15); (2) 50 μ g of BCNU from BCNU-containing microparticles (n=15); (3) 100 μ g of BCNU from BCNU-containing microparticles (n=15); and (4) 100 μ g of a BCNU bolus (n=15). Control animals receiving no implant were also assessed. The results are presented in Table 2 and represented graphically in Figure 7.

The results suggest that animals receiving BCNU-containing microparticles into the peritumoral tissue show enhanced survival when compared to animals receiving the same dose of BCNU-containing microparticles directly into the tumor.

TABLE 2

Treatment Group	Median Survival (Days Post Tumor Implantation)	Maximum Survival (Days Post Tumor Implantation)
No Treatment	20	24
Bolus (100 μ g) Intratumorally	20	24
Microparticles (10 μ g) Intratumorally	20	25
Microparticles (50 μ g) Intratumorally	21	24
Microparticles (100 μ g) Intratumorally	25	33
Bolus (100 μ g) Peritumorally	25	41
Microparticles (10 μ g) Peritumorally	21	32

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Microparticles (50 µg) Peritumorally	31	48
Microparticles (100 µg) Peritumorally	41	55

EXAMPLE 9: CELL MAINTENANCE AND IMPLANTATION OF MATB-III CELLS

MATB-III cells, originally derived from a rat mammary carcinoma (ATCC# CRL-1666), were grown and maintained as a suspension culture in McCoy's 5A Medium supplemented with 10% fetal bovine serum, 20mM HEPES and 1/2x penicillin-streptomycin/fungizone. Cells were harvested and centrifuged at 1500g for 4 minutes at 10 °C prior to suspending at a density of 2×10^6 cells/mL in HEPES-buffered serum-free media containing 1.2% methyl cellulose. For implantation, rats were briefly anesthetized with a combination of O₂/CO₂. MATB-III cells (1×10^6 cells/200µL) were injected subcutaneously into the right rear flank using a 21 gauge needle attached to a 1 mL syringe. All tumors were allowed to grow for 7 days at which time animals with tumors that had reached a size of approximately 140 mm² were used in dosing studies. Tumors were measured every 2-4 days and any animal bearing a tumor equal to or greater than 900 mm² was sacrificed.

EXAMPLE 10: PREPARATION OF CARBOPLATIN LOADED AND 5-FU LOADED MICROPARTICLES

Carboplatin loaded and blank microparticles were prepared according to Example 2, with a carboplatin loading density of 10% (w/w). Microparticles containing 5-fluorouracil at a loading density of 10% (w/w) were also prepared according to the method described in Example 2.

EXAMPLE 11: BOLUS CHEMOTHERAPY AND IMPLANTATION OF
SUSTAINED RELEASE CHEMOTHERAPEUTIC MICROPARTICLES IN A
RAT MODEL OF SOLID TUMOR

5 Seven days following tumor implantation as described above in Example 9, animals received injections of microparticles containing carboplatin or 5-FU (10% w/v) prepared as described above, or a bolus injection of carboplatin or 5-FU, directly into the center of the tumor or into the peritumoral tissue. Microparticles were formulated to release carboplatin or 5-FU in a sustained fashion over about a
10 two week period. Bolus injections into the center of the tumor were made in a volume of 150 μ L using a 20 gauge needle attached to a 200 μ L Hamilton syringe. For bolus injections within the 6 sites of the tumor perimeter, animals received the same total amount of carboplatin or 5-FU that was injected into the center of the tumor, except that it was equally divided into 6 separate 25 μ L aliquots.

15 For injections of sustained release microparticles, a total of 50 mg of microparticles were suspended (30% PLG w/v) in a solution of 0.9% saline, 0.1% Tween and 3.0% carboxymethylcellulose (low viscosity). Animals receiving injections into the center of the tumor received 150 μ L of the suspension, while animals receiving microparticles within the peritumoral tissue received the same
20 total amount of sustained release carboplatin or 5-FU that was delivered directly into the center of the tumor, except that it was equally divided into separate 25 μ L aliquots for each of the 6 injection sites. The injection sites were determined by first making a small incision in the skin overlying the tumor. Once the peripheral tumor was visualized, microparticles were injected into six discrete sites as follows: Four
25 sites equally distributed along the equator of the tumor and one site at each of the two distal poles of the tumor.

 In all cases, the microparticles were injected using a 20 gauge needle as described above. For sustained release chemotherapy, animals received a total of 0.1, 0.5, 1.0, or 5.0 mg of carboplatin or 5-FU. Control animals received either no
30 treatment or blank microparticles. Identical amounts of microparticles were injected in all cases by adding blank microparticles to the suspension. The different treatment groups and the numbers of animals in each are listed below in Table 3.

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TABLE 3

Treatment	Number of Subjects (n)	Statistical Significance (vs no treatment)
No Treatment	12	
Carboplatin Bolus (5.0mg) Center	12	p>0.1
Carboplatin PLG (5.0mg) Center	12	p>0.1
Blank PLG Perimeter	11	p>0.1
Carboplatin Bolus (5.0mg) Perimeter	12	p>0.1
Carboplatin PLG (0.1mg) Perimeter	11	p>0.1
Carboplatin PLG (0.5mg) Perimeter	11	p>0.1
Carboplatin PLG (1.0mg) Perimeter	10	p<0.01
Carboplatin PLG (5.0mg) Perimeter	12	p<0.001
5-FU Bolus (5.0mg) Center	12	p>0.1
5-FU PLG (5.0mg) Center	12	p>0.1
Blank PLG Perimeter	12	p>0.1
5-FU Bolus (5.0mg) Perimeter	12	p>0.1
5-FU PLG (0.1mg) Perimeter	15	p<0.05
5-FU PLG (0.5mg) Perimeter	15	p<0.01
5-FU PLG (1.0mg) Perimeter	15	p<0.001
5-FU PLG (5.0mg) Perimeter	15	p<0.001

Statistical analyses were performed using a repeated measures ANOVA with tumor size treated as the repeated measure. Acceptable statistical significance was established as p<0.05.

As can be seen in Figure 8 and from the data above, the highest dose carboplatin (5mg) delivered as a bolus injection had no effect on tumor growth (relative to no treatment) independent of whether the injection was made into the

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center of the tumor or into 6 sites within the peritumoral tissue. Sustained release carboplatin (5 mg total) delivered to the tumor center was also ineffective in suppressing tumor growth as these animals also exhibited tumor growth comparable to animals receiving no treatment. In contrast, injections of sustained release microparticles within the peritumoral tissue produced a dose-related suppression in tumor growth. Low doses of carboplatin (0.1 and 0.5 mg) did not significantly alter tumor growth, while higher doses (1.0 and 5.0 mg) significantly suppressed the growth of MATB-III tumors. Injections of blank microparticles within the peritumoral tissue were without effect.

As can be seen in Figure 9 and from the data above, the highest dose of 5-FU (5mg) delivered as a bolus injection did not suppress tumor growth whether the injection was made into the center of the tumor or into 6 sites within the peritumoral tissue. In addition, sustained release 5-FU (5 mg total) delivered to the tumor center had no effect on tumor growth. In contrast, a dose-related suppression of tumor growth was observed when the sustained release microparticles were injected into 6 sites within the peritumoral tissue. Injections of blank microspheres within the peritumoral tissue were without effect.

Together, these data complement and extend the results achieved with brain tumors by demonstrating: 1) the superiority of sustained release over bolus chemotherapy and 2) the superiority of peritumoral administration over intratumoral administration of microparticles containing a chemotherapeutic agent.

EXAMPLE 12: SEQUENTIAL ADMINISTRATION OF 5-FU AND CARBOPLATIN CONTAINING MICROPARTICLES IN A RAT MODEL OF SOLID PERIPHERAL TUMORS

Following the initial treatment at 7 days post implantation of the MATB-III cells, the animal were again injected (21 days post implantation) into the peritumoral tissue as described above with carboplatin or 5-FU containing microparticles.

Figure 10 is a graph of the effect of this sequential administration on tumor growth.

A further reduction in tumor growth was observed for both the carboplatin and 5-FU sustained release compositions following a second peritumoral injection of microparticles containing either carboplatin or 5-FU.

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While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

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CLAIMS

What is claimed is:

1. A method of treating a patient suffering from a solid tumor, comprising administering to the peritumoral tissue an effective amount of a sustained release composition comprising a biocompatible polymer and at least one chemotherapeutic agent dispersed within the polymer.
2. The method of Claim 1 wherein the solid tumor is a tumor of the brain, prostate, breast, colon, lung, kidney, bladder, liver, bone, head, neck, stomach, larynx, esophagus, cervix, rectum, uterus, skin, endometrium, pancreas or testes.
3. The method of Claim 2 wherein the solid tumor is a tumor of the brain.
4. The method of Claim 3 wherein the tumor of the brain is a glioma.
5. The method of Claim 1 wherein the sustained release composition comprises microparticles.
6. The method of Claim 5 wherein the microparticles are administered by injection into the peritumoral tissue.
7. The method of Claim 1 wherein the sustained release composition is in the form of wafers, rods, filaments, or combinations thereof.
8. The method of Claim 7 wherein the sustained release composition is administered by injection into the peritumoral tissue.
9. The method of Claim 1 wherein the chemotherapeutic agent is selected from the group consisting of: antimetabolites, immunomodulators, cytotoxic agents, antibiotic derivatives, nitrogen mustard derivatives, antiangiogenic

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agents, receptor antagonists, receptor ligands, stimulators, viral vectors, and combinations thereof.

10. The method of Claim 9 wherein the chemotherapeutic agent is a cytotoxic agent.
11. The method of Claim 10 wherein the cytotoxic agent is in combination with one or more chemotherapeutic agents.

- 10
12. The method of Claim 9 wherein the chemotherapeutic agent is carboplatin, cisplatin, carmustine, paclitaxel, doxorubicin, adriamycin, lomustine, teniposide, etoposide, 0⁶-benzylguanine, vincristine, vinblastine, vinorelbine, gemcitabine, cyclophosphamide, temasolamide, 5-fluorouracil, 4-HC, methotrexate or combinations thereof.

13. The method of Claim 1 wherein the polymer of the sustained release composition is selected from the group consisting of: poly(lactides), poly(glycolides), poly(lactide-co-glycolides), poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polycaprolactone, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyorthoesters, polycyanoacrylates, poly(p-dioxanone), poly(alkylene oxalate)s, biodegradable polyurethanes, blends thereof and copolymers thereof.

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14. The method of Claim 13 wherein said polymer comprises poly(lactide-co-glycolide).

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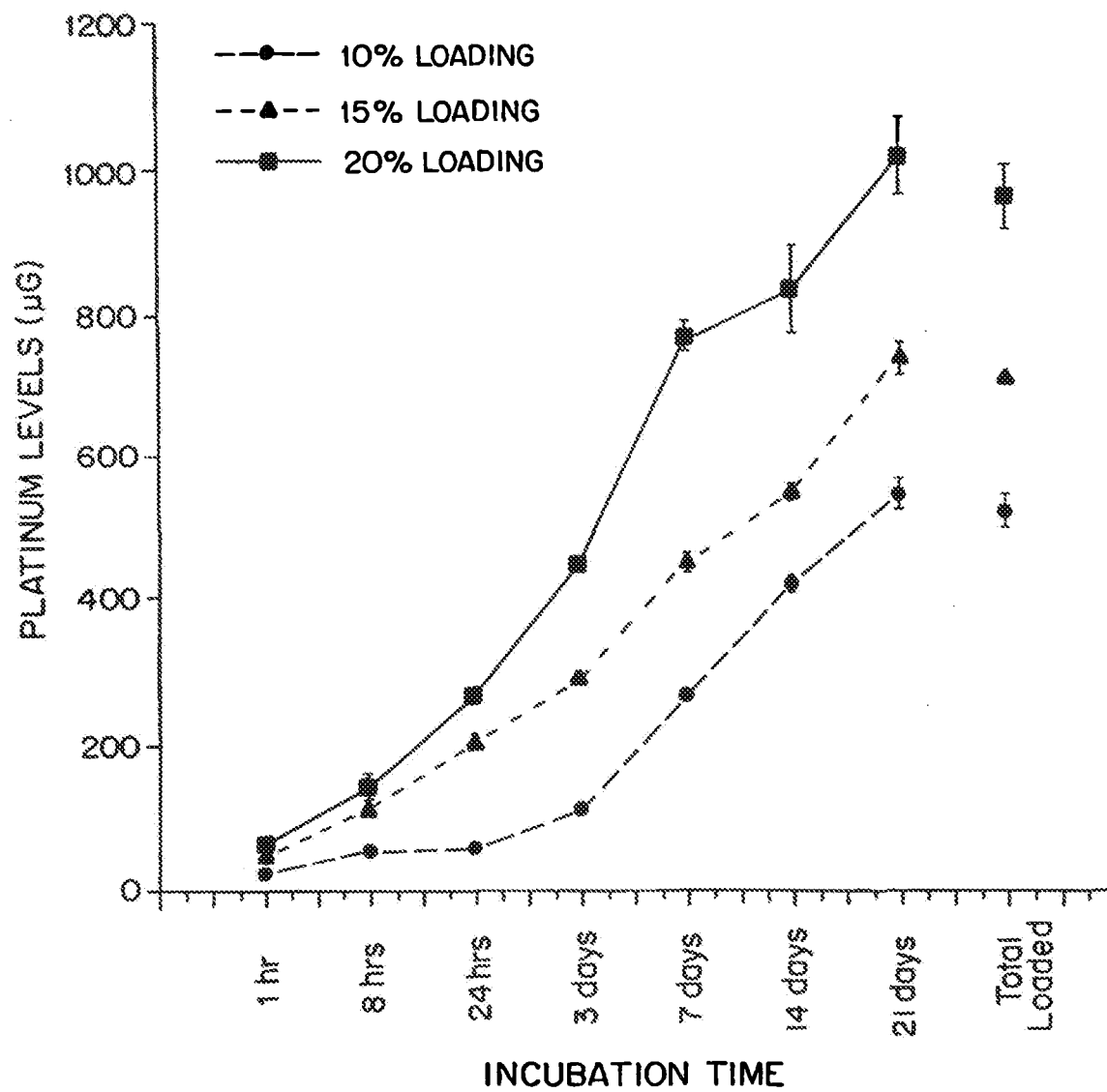


FIG. 1

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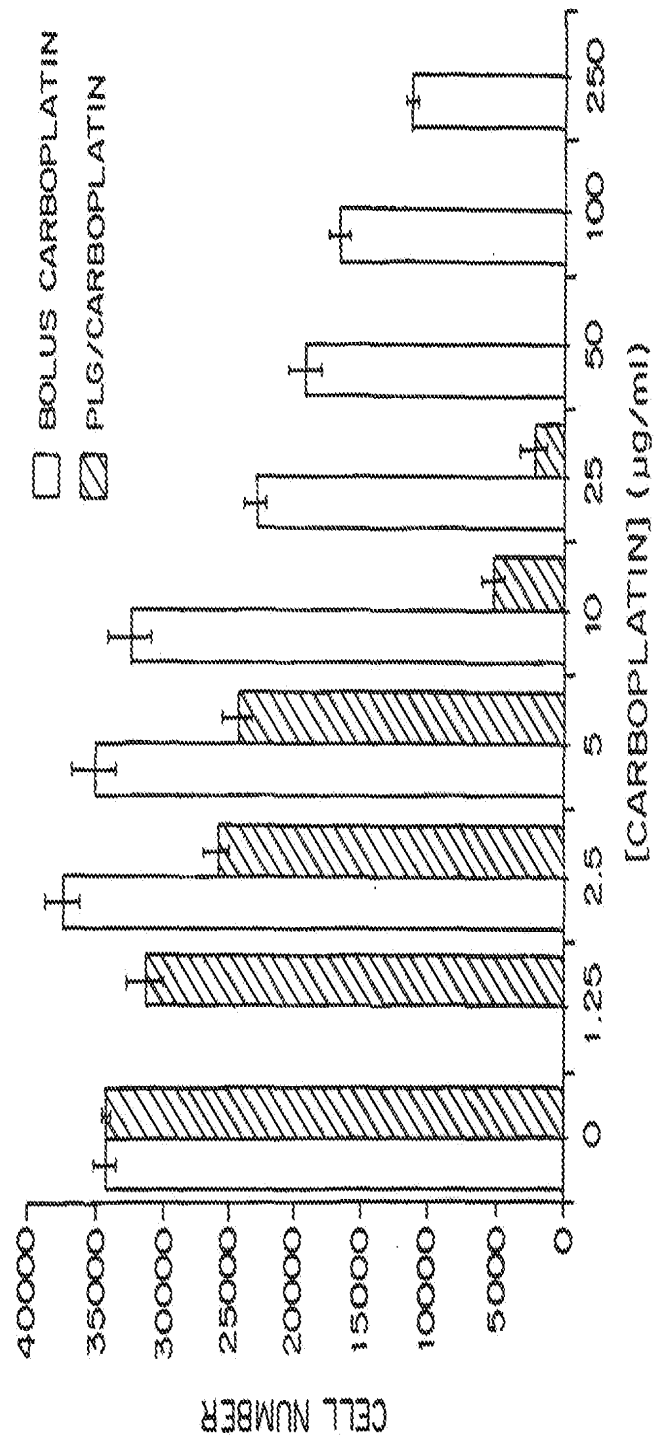


FIG. 2

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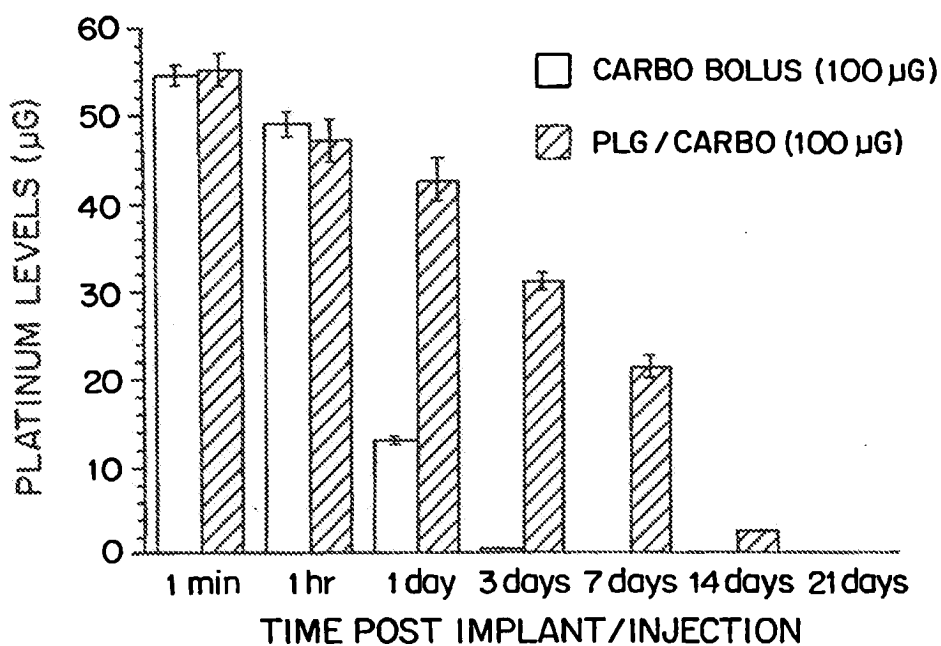


FIG. 3A

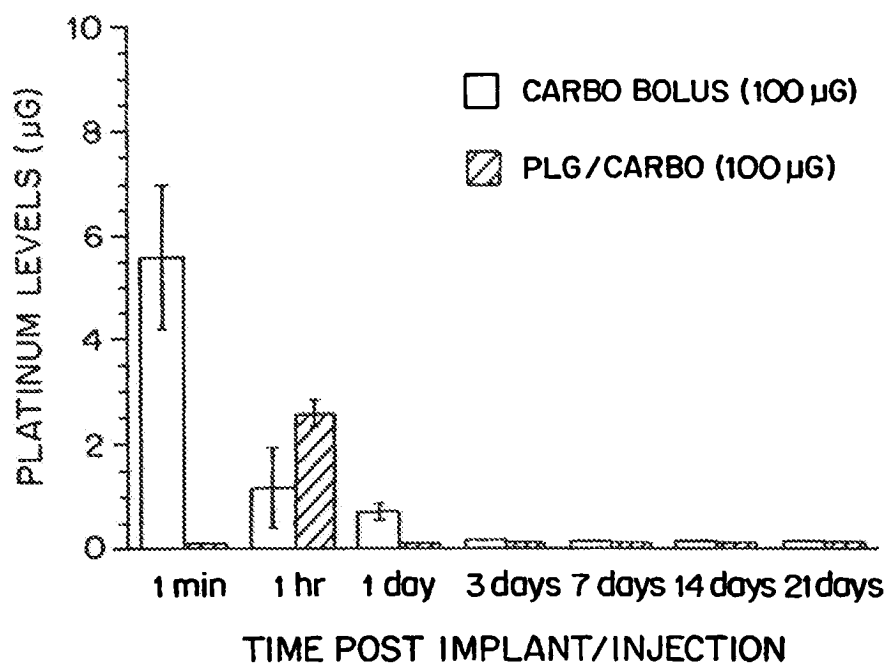


FIG. 3B

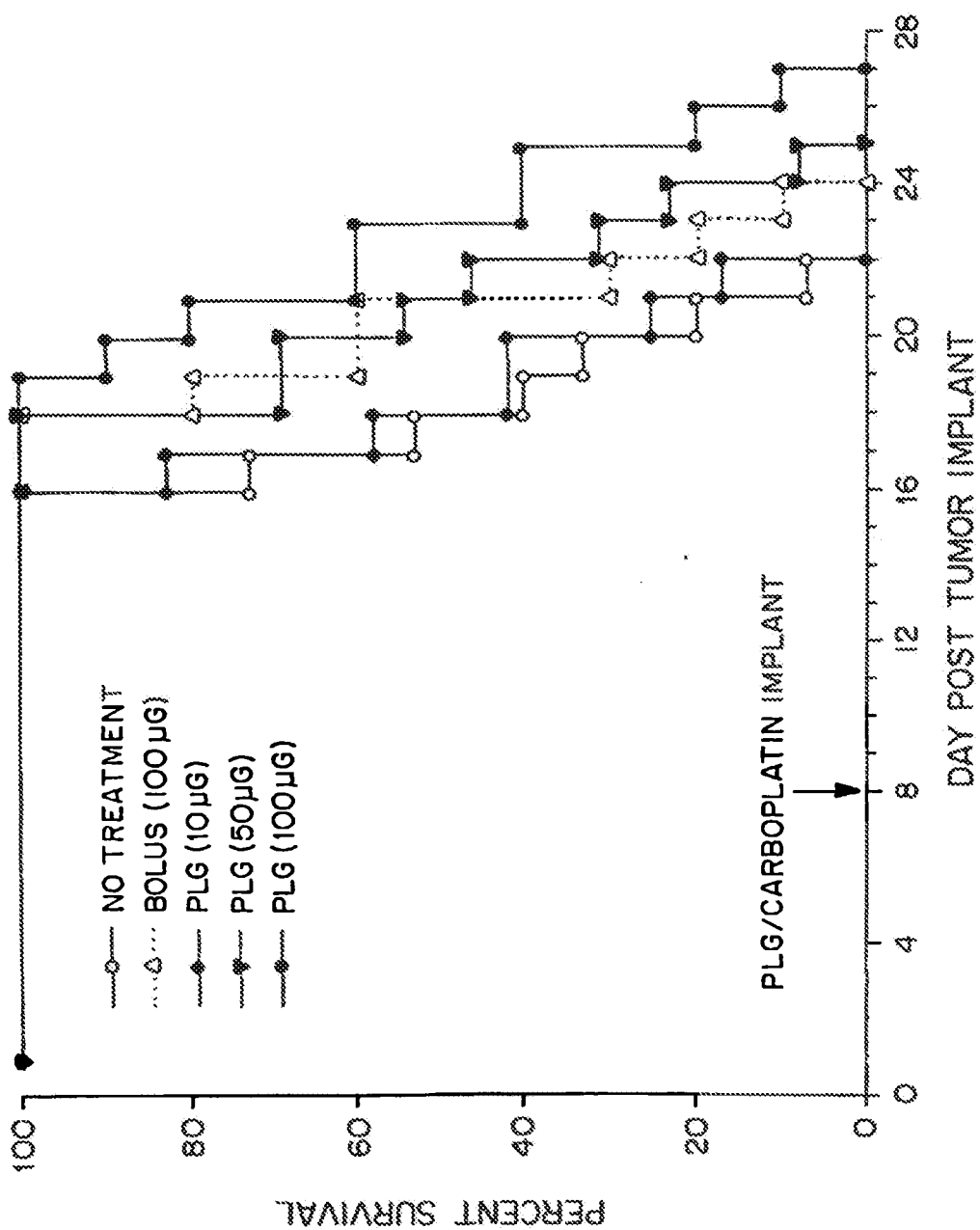


FIG. 4

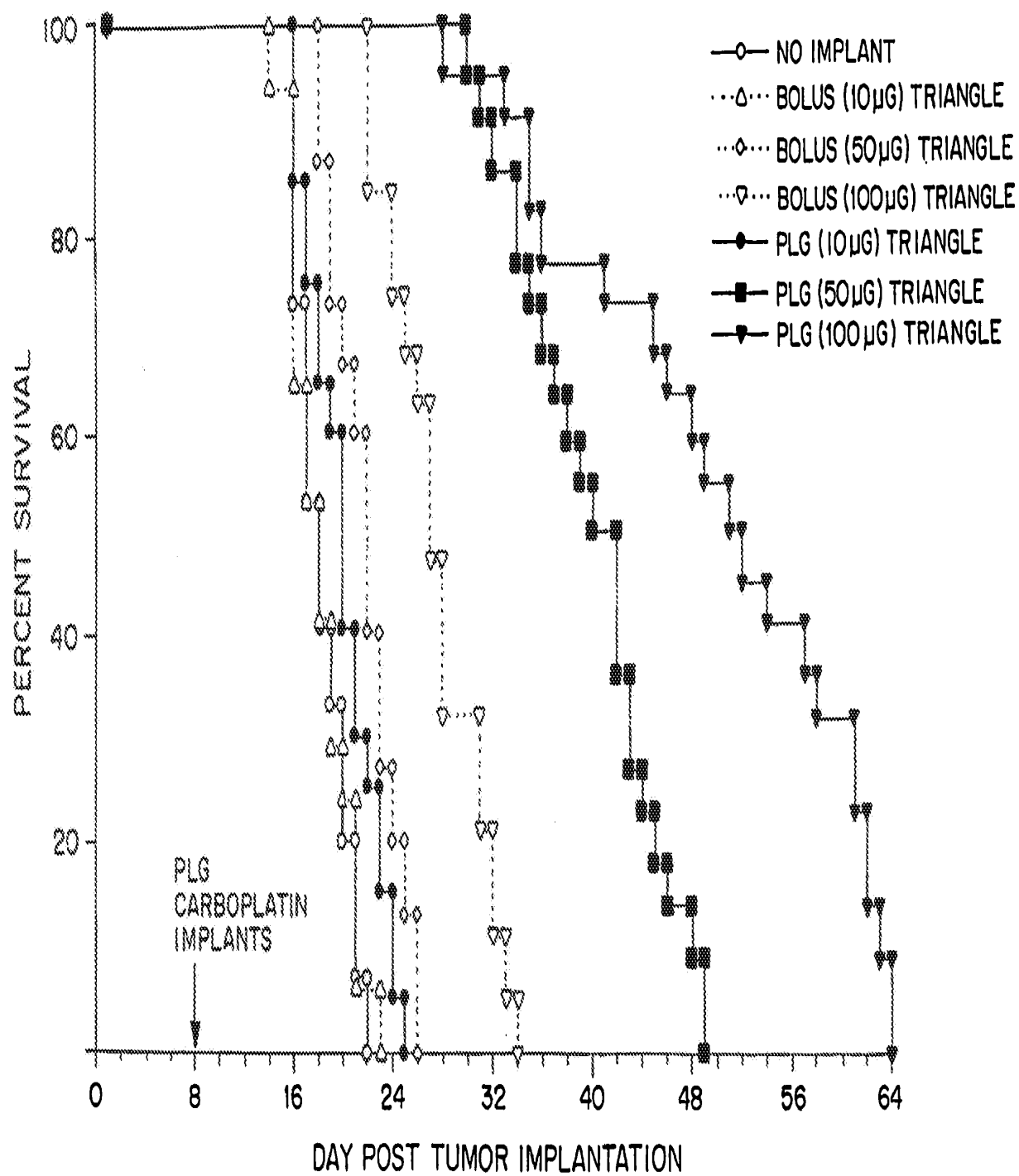


FIG. 5

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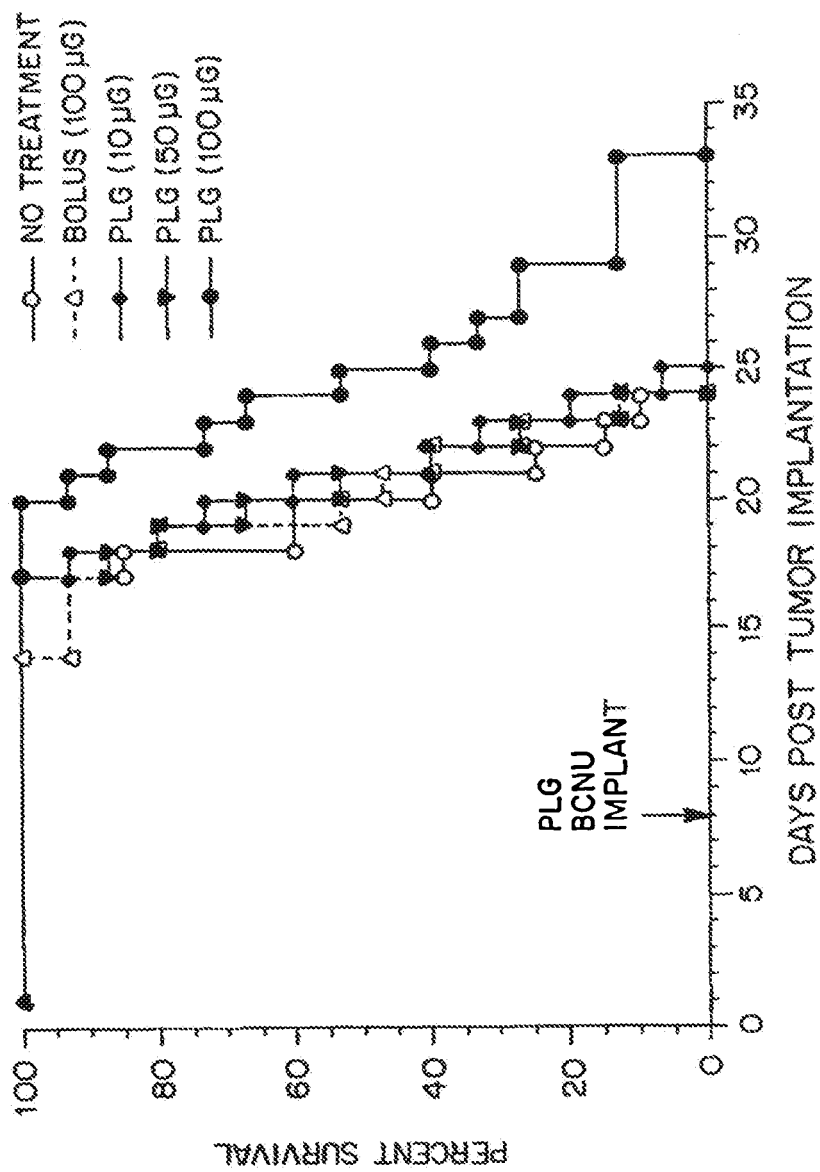


FIG. 6

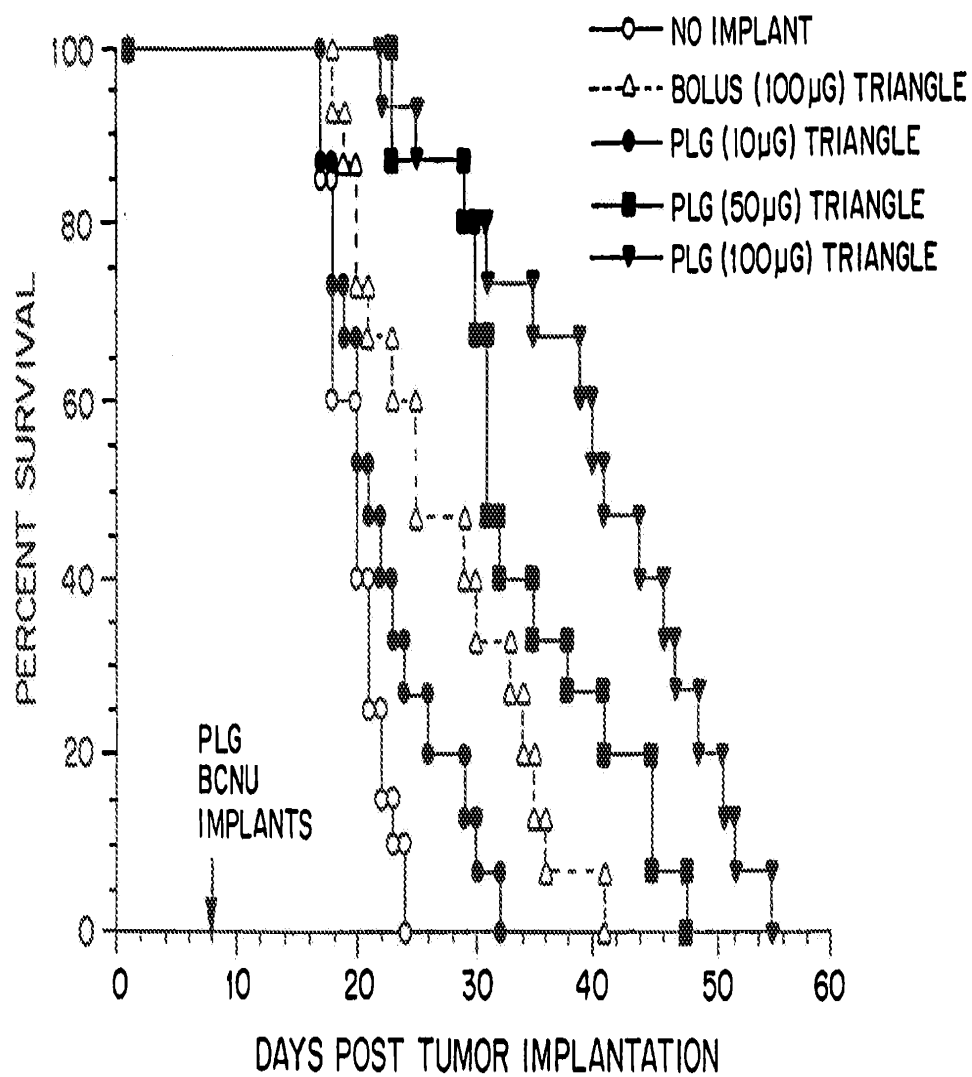


FIG. 7

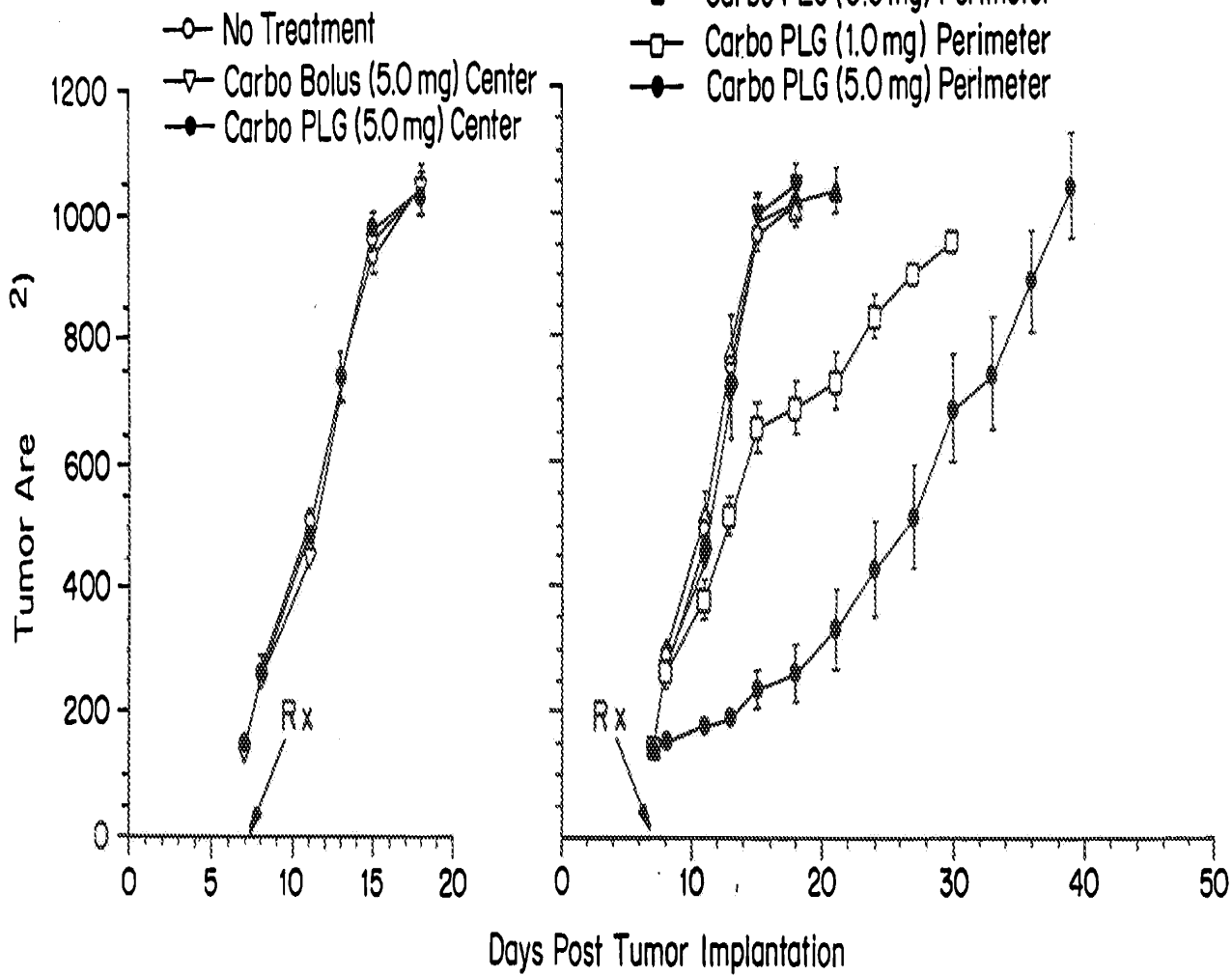


FIG. 8

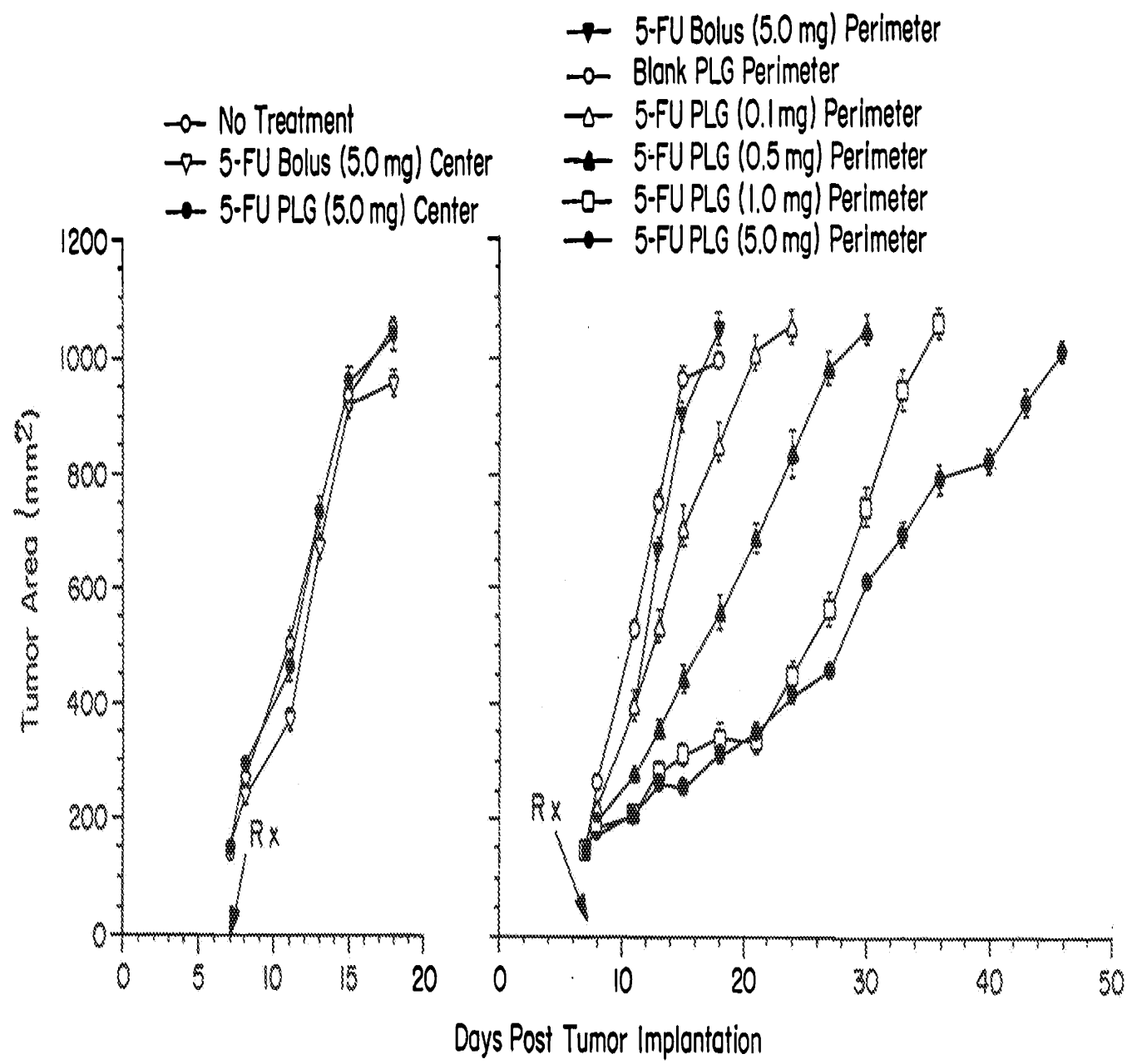


FIG. 9

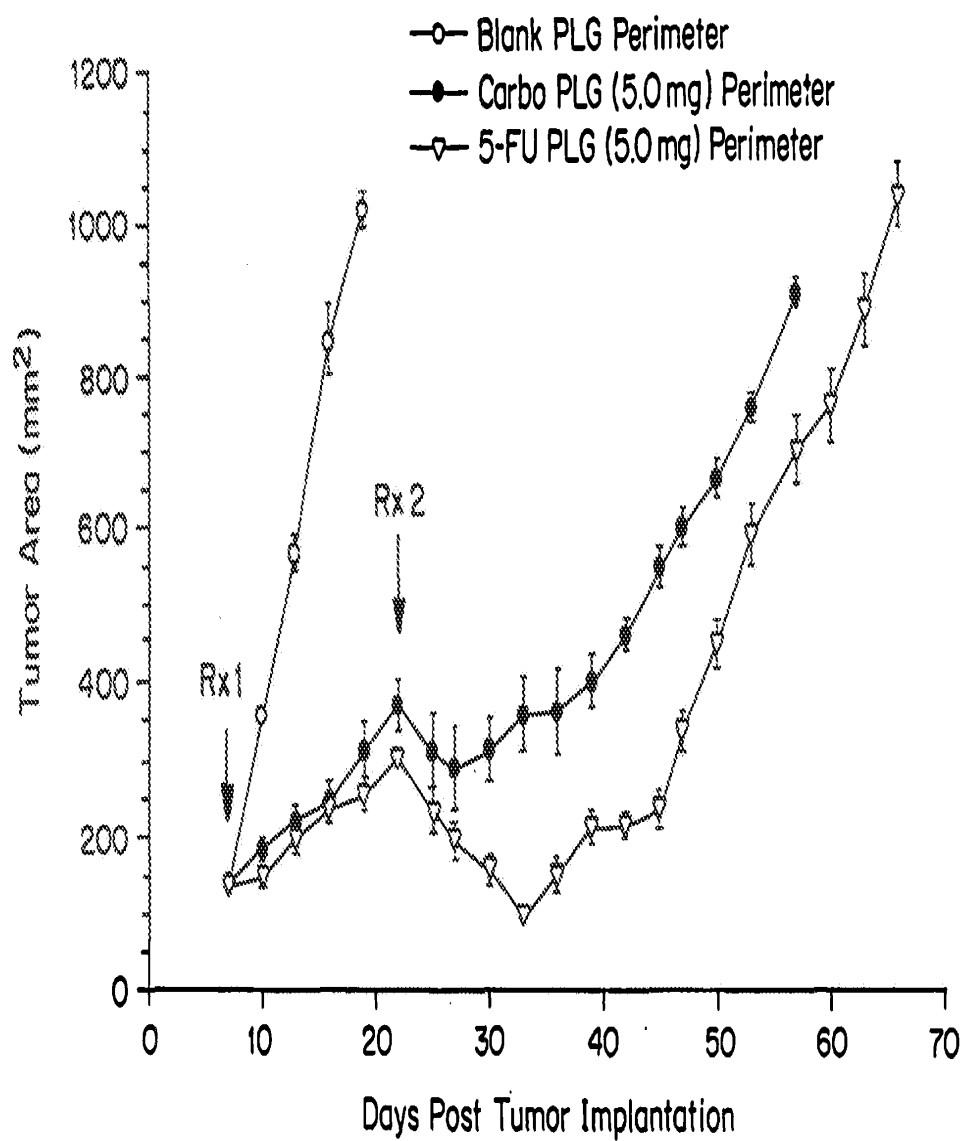


FIG. 10

INTERNATIONAL SEARCH REPORT

Int. No. Application No
PCT/US 00/21919

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 688 530 A (D. BODMER ET AL.) 18 November 1997 (1997-11-18) claim 3 column 3, line 26 - line 42 column 7, line 38 - line 61 column 8, line 34 - line 40 column 12, line 10 - line 14 column 12, line 21 - line 24 column 12, line 32 - line 33	1,2,5,6, 9,13,14
X	EP 0 145 240 A (TAKEDA) 19 June 1985 (1985-06-19) claims 1,4,6,9 page 5, line 1 - line 8 page 9, line 13 - line 22 page 16, line 8 - line 28 page 19, line 6 - line 7	1,5,6,9, 12-14

-/-

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

5 January 2001

Date of mailing of the international search report

15/01/2001

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Scarponi, U

INTERNATIONAL SEARCH REPORT

Inventor: application No
PCT/US 00/21919

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 42940 A (ALKERMES) 20 November 1997 (1997-11-20) claims 1-3,11-13,17,18,35-39,42,44-46,55 page 9, line 10 - line 17 page 13, line 8 - line 10 page 13, line 16 - line 21 page 15, line 7 - line 12	1,5-9, 13,14
X,P	WO 00 41678 A (GUILFORD) 20 July 2000 (2000-07-20) claims 1,4,6,7,20,21,39,40,50,52-60,63-65,78,79,9 7,98 claims 110-121,124-126,139,140,158,159,171-181	1,2, 5-10,12, 13

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inventor: application No
PCT/US 00/21919

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